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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/770,901	01/26/2001	Joaquina Faour	PHUS-28	7749

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EXAMINER	
JIANG, SHAOJIA A	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/770,901	FAOUR ET AL.	
	Examiner	Art Unit	
	Shaojia A Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 4-6, 10-15, 18-38, 43-45, and 48-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,10-15,18-38,43-45,48,50,53,54 and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/14/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 14, 2004 has been entered.

This Office Action is a response to Applicant's request for continued examination (RCE) filed April 14, 2004, and amendment and response to the Final Office Action (mailed January 13, 2004), filed April 14, 2004 wherein claims 1, 4-6, 10-15, 18-38, 43-45, and 48-54 have been amended; claims 2-3, 7-9, 16-17, 39-42, and 46-47 are cancelled; claim 55 is newly submitted.

Currently, claims 1, 4-6, 10-15, 18-38, 43-45, and 48-55 are pending in this application.

Claims 1, 4-6, 10-15, 18-38, 43-45, and 48-55 are examined on the merits herein.

Applicant's amendment filed April 14, 2004 with respect to the rejection of claims 1, 4-5, 10, 13-14, and 18-38, and claims 8, 17, and 40 made under 35 U.S.C. 112 first paragraph for containing new subject matter, i.e., reciting "wherein inhibitor binds COX-II receptors selectively over COX-I receptors or binds COX-II receptors specifically" and

"..providing an additive or synergistic therapeutic effect" of record stated in the Office Action dated January 13, 2004 have been fully considered and found persuasive to remove the rejection since these recitations have been removed.

Applicant's remarks filed April 14, 2004 with respect to the rejection of claims 12, 29, 34, 36, and 52-53 under 35 U.S.C. 112 first paragraph for containing new subject matter, i.e., reciting "release at a faster rate than the muscle" and "..released at a slower" of record stated in the Office Action dated January 13, 2004, have been fully considered and found persuasive to remove the rejection since Figure 1 and 2 of the originally filed specification are seen to provide support these recitations.

The references in the supplemental IDS filed April 14, 2004 have provided the chemical names for NS-398, DUP-697, SC-57666, and T-614, have been fully considered and found persuasive to remove the rejection as to these chemical names.

Applicant's amendment amending claims 1, 4-5, 10, 13-14, and 18-38, filed April 14, 2004 with respect to the rejection made under 35 U.S.C. 112 first paragraph for lack of scope of enablement of record stated in the Office Action dated January 13, 2004 has been fully considered and is found persuasive to remove the rejection since the particular COX-II inhibitors and the particular muscle relaxants have been recited in these claims. Therefore, the said rejection is withdrawn.

Applicant's amendment amending claims 1 and 4-8, filed April 14, 2004 with respect to the rejection made under 35 U.S.C. 112 first paragraph for lack of

enablement, i.e., "synergistic therapeutic effect" of record stated in the Office Action dated January 13, 2004 has been fully considered and is found persuasive to remove the rejection since the recitation "synergistic" has been removed from these claims. Therefore, the said rejection is withdrawn.

Applicant's remarks filed April 14, 2004 and Attachments A-D submitted September 23, 2002, with respect to the rejection of claims 12, 29, 34, 36, and 52-53 made under 35 U.S.C. 112 second paragraph for the indefinite recitations, i.e., "release at a faster rate than the muscle" and "..released at a slower.." of record stated in the Office Action dated January 13, 2004 have been fully considered and found persuasive to remove the rejection since one of ordinary skill in the art would understand the terms. Therefore, the said rejection is withdrawn.

The following is the new ground(s) of rejection(s).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-6, 10-15, 18-38, 43-45, 48 and 55 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification such as the working example, Figure 1-2, and the evidence provided by Applicant in the declaration of Ethel C. Feleder under 37 C.F.R. 1.132 filed on October 23, 2003 and during the interview February 23, 2004, while being enabling for a single combination, i.e., rofecoxib (a COX-II inhibitor) and pridinol (a muscle relaxant) being tested to be administered to a host and showing additive effect employed in claimed composition herein, does not reasonably provide enablement for the employment all COX-II inhibitors in combination with all muscle relaxants recited in the claims herein.

The instant specification such as the working example, Figure 1-2, and the evidence provided by Applicant in the declaration of Ethel C. Feleder under 37 C.F.R. 1.132 filed on October 23, 2003 and the evidence presented during the interview February 23, 2004, fail to provide sufficient information that would allow the skilled artisan to **fully** practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to pharmaceutical composition comprising the combination the COX-II inhibitor in combination and the muscle relaxant of for the particular treatments.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability and the presence or absence of working examples and the quantity of experimentation necessary as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the single combination, i.e., rofecoxib (a COX-II inhibitor) and pridinol (a muscle relaxant) was tested in vivo, and shows additive effect. However, claims 1 and 10 recite a widely varying compounds and their combinations. More importantly, they do not share common core structures, i.e., they do not have the central and critical core of structure in common. They are separate and distinct compounds and classified into different subclasses of class 514, for example, COX-II inhibitors, rofecoxib or celecoxib having pyrazole in 514/406; N-(2-Cyclohexyloxy-4-nitrophenyl)methanesulfonamide in 514/728; 5 -bromo-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]- thiophene in 514/438; muscle relaxants, Pridinol having piperidne in 514/315; Baclofen containing no piperidne but having a γ-amino-acid in 514/561; Alosetron in 514/291 and 406 for example. See their structures provided by CAS STN Registry (PTO-892).

Thus, COX-II inhibitors, rofecoxib or celecoxib; N-(2-Cyclohexyloxy-4-nitrophenyl)methanesulfonamide; 5 -bromo-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]- thiophene; are **not** deemed to have same or substantial similar physical, chemical, biological and physiological properties or activities. In the same regard, muscle relaxants, Pridinol, Baclofen, and Alosetron are not deemed to have same or substantial similar activities.

Therefore, one of skill in the art would clearly recognize that the evidence for the single combination, i.e., rofecoxib (a COX-II inhibitor) and pridinol (a muscle relaxant) is deemed not to represent all widely varying combinations encompassed by the claims. Therefore the enabling evidence for the single combination of rofecoxib and pridinol is not sufficient in support of all other various combinations.

Moreover, as pointed out in the text book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" (9th ed, 1996, of record, page 51 in particular) regarding possible drug-drug interactions. This book teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right column of page 51) (emphases added).

In the instant case, in the absence of factual evidence for all other widely varying combinations, one of skill in the art would not be able to fully predict possible beneficial or adverse drug-drug interactions occurring with theses combinations to be administered to a human. Thus, the teachings of the book clearly support that the instant claimed invention is highly unpredictable.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation*, with no assurance of success.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 33, 50, and 53-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitations "an acidifying agent, adsorbent, alkalizing agent, antioxidnnt, buffering agent, ...solvent, oil, soap, detergent" renders these claims indefinite. As noted in MPEP 2111, during patent examination, claims are given their **broadest**

reasonable interpretation. Hence, one of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired as to what "an acidifying agent, adsorbent, alkalizing agent, antioxidant, buffering agent, ...solvent, oil, soap, detergent" in particular, since these recitations encompass hundreds or thousands compounds or agents. Therefore, the claims are indefinite as to the recitations encompassed thereby.

The recitation "a subject" in claims 53 renders the claim indefinite. The recitation "a subject" is not clearly defined in the claims or specification. One of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired as to what "a subject" would be, for example, that the term " subject " would be a single cell, any biological system, an animal or a human, or any non- biological system. Thus, one of ordinary skill in the art could not interpret encompassed thereby.

Claims 53-54 recite the limitation "**at least** one of the COX-II inhibitor" which reads on one or more than one COX-II inhibitors. There is insufficient antecedent basis for this limitation in the claim, since claim 49 recites "**a** COX-II inhibitor selecting from..". Thus, only one COX-II inhibitor is claimed in combination with pridinol in the independent claim 49.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-6, 10-15, 18-38, 43-45, 48 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gans et al. or Futaki et al. (PTO-1449 submitted April 14, 2004) in view of Okada et al. (5,476,663, of record).

Gans et al. discloses that DuP 697 having chemical name, 5 -bromo-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]- thiophene, is a known anti-inflammatory agent to be useful in a composition and a method of treating inflammatory conditions. See the abstract.

Gans et al. discloses that NS-398 having chemical name, N-(2-Cyclohexyloxy-4-nitrophenyl)methanesulfonamide, is a known non-steroidal anti-inflammatory agent to be useful in a composition and a method of treating inflammatory conditions. See the abstract.

The prior art does not expressly disclose that the employment of the particular COX-II inhibitor such as DuP 697 or NS-398 in combination with the particular muscle relaxant such as pridinol in a pharmaceutical composition or dosage. The prior art does also not expressly disclose the effective amounts of active agents in the composition herein to be administered, e.g., the weight ratio of the COX-II inhibitor and the muscle relaxant.

Okada et al. teaches that a muscle relaxant such as pridinol is useful in combination with analgesic and/or anti-inflammatory drugs (see col.3 lines 13-28).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ a COX-II inhibitor such as DuP 697 or NS-398 in

combination with a muscle relaxant such as pridinol in a pharmaceutical composition or dosage, and to optimize the effective amounts of active agents in the composition herein to be administered, e.g., the weight ratio of a COX-II inhibitor and a muscle relaxant.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ a COX-II inhibitor such as DuP 697 or NS-398 in combination with a muscle relaxant such as pridinol in a pharmaceutical composition or dosage since COX-II inhibitors such as DuP 697 or NS-398 are known to be useful in a composition or dosage and a method of treating inflammatory conditions. Moreover, muscle relaxants such as pridinol are well known to be useful alone or in combination with conventional analgesics for the treatment of inflammatory conditions. Therefore, one of ordinary skill in the art would have reasonably expected that combining a COX-II inhibitor such as DuP 697 or NS-398 and a muscle relaxant such as pridinol known useful for the same purpose in a composition to be administered would improve the therapeutic effect for treating inflammatory conditions such as pain.

Since all active composition components herein are known to useful to treat pain, it is considered prima facie obvious to combine them into a single composition to form a third composition useful for the very same purpose, treating inflammatory conditions. At least additive therapeutic effects would have been reasonably expected. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980).

Additionally, one of ordinary skill in the art would have been motivated to optimize the effective amounts of active ingredients in the composition because the

optimization of known amounts of known active agents to be administered is considered well within the skill of artisan.

It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Applicant's remarks filed on April 14, 2003, especially Table 1 such as p value at page 8-11, providing the further explanation for the evidence in the declarations of Ethel C. Feleder under 37 C.F.R. 1.132 for the particular combination, i.e., rofecoxib (a COX-II inhibitor) and pridinol (a muscle relaxant) being tested to be administered to mouse and showing unexpected effect, have been considered and found persuasive to overcome the 103(a) rejection of claims 49-54.

However, the evidence is not commensurate in scope with claims 1, 4-6, 10-15, 18-38, 43-45, 48 and 55 and does not demonstrate criticality of a claimed range of the widely varying combinations as discussed in the previous Office Action January 13, 2004. See MPEP § 716.02(d). For the above stated reasons, claims 1, 4-6, 10-15, 18-38, 43-45, 48 and 55 are properly rejected under 35 U.S.C. 103(a).

Therefore, claims 49, 51, and 52 are seen allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Anna Jiang, Ph.D.
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June 22, 2004